



MYLAN TECHNOLOGIES INC.

December 10, 2004

**VIA FEDERAL EXPRESS**

Division of Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

**RE: Comments of Mylan Technologies Inc. on Docket No. 2004P-0506:  
To Require Comprehensive Risk Minimization Programs for Fentanyl  
Matrix Systems and to Treat Fentanyl Matrix Systems as Different Dosage  
Forms Than Fentanyl Reservoir Systems**

Dear Sir or Madam:

Mylan Technologies Inc. ("Mylan") submits these comments in response to the above-referenced Citizen Petition filed by Alza Corporation ("Alza") on November 12, 2004 (the "Petition").

Mylan has an interest in the Petition because Mylan has submitted an abbreviated New Drug Application ("ANDA") for a generic fentanyl transdermal system ("FTS") and Alza has recommended that FDA restrict the approval of Mylan's ANDA in ways that would unnecessarily handicap Mylan's introduction of its generic fentanyl transdermal system.

Alza's Petition should be denied because it asks FDA to draw unprecedented distinctions between a generic product and a referenced product based on nothing but speculation by the company that would directly benefit from those distinctions. As addressed in detail herein, FDA has never considered the fact that two products have different rate controlling mechanisms to be a reason to categorize those products as different dosages forms. For transdermal systems, FDA has considered bioequivalence and equivalence in delivery rate, not the structure of the transdermal system, as the critical factors in approving generic products. To do so would be contrary to the purposes of the Hatch-Waxman Act by minimizing generic competition for Duragesic® forever and by depriving American patients of Mylan's matrix design that avoids the dangers of leakage and has other practical advantages. Alza has presented no evidence that the design differences between Duragesic® and the Mylan FTS create any performance differences that could conceivably warrant such a distinction between the two products.

Alza's request that FDA take the equally unprecedented step of requiring Mylan's generic fentanyl transdermal matrix systems to be governed by a risk minimization plan when Duragesic® is subject to no such plan is not justified and unsupported by any evidence of the

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need for such a plan.<sup>1</sup> There is simply no basis for Alza's assertion that there is an increased risk of abuse and diversion arising from use of the Mylan FTS system. In fact, as even Alza has to concede, the Mylan matrix system makes it more difficult for would-be abusers to obtain fentanyl in an immediately available form and eliminates the significant danger created by the potential leakage of fentanyl-laden gel from the reservoir of the Duragesic® system. Because there is no basis for subjecting the Mylan FTS to the restrictions Alza proposes, Mylan respectfully requests that the Alza's Petition be denied.

- **Alza's Competitive Interest in the Actions Requested Warrants a Skeptical View of the Petition.**

Alza goes to great pains to assert in its Petition that it "supports FDA approval of generic fentanyl transdermal products" and that "none of the actions requested in [Alza's] petition would prevent FDA from approving such products." Alza Petition at 1. The disingenuousness of Alza's Petition is apparent. Alza's two "actions requested" have two plain goals: to delay FDA approval of generic competitors and to interfere with substitution of approved generic fentanyl transdermal systems for Duragesic®.

On the very threshold of facing generic competition in the U.S. market for its immensely profitable Duragesic® product, Alza is making this last-ditch effort to prevent Mylan from competing effectively with Duragesic®. Alza's Petition was obviously timed to maximize the potential impact on the final approval of the Mylan FTS with the aim of extending even further Alza's monopoly on the sale of fentanyl transdermal systems. Alza has been aware for years that Mylan's ANDA product is a matrix system, yet has raised this alleged safety concern only now that it has run out of other ways of blocking competition from the Mylan FTS.<sup>2</sup>

Alza's Petition is designed as part of an effort to create a last minute flurry of activity within the FDA attempting to block or interfere with approval of the Mylan FTS. See Docket Nos. 2004P-0340, 2004:-0472, and 2004P-0540. Alza's Petition largely recycles the arguments made in those petitions, which have already been rebutted in Mylan's responses to those petitions. These types of repetitive and unfounded attacks on a product nearing approval are a misuse of the petition process, one about which the FTC has specifically expressed concerns. See Comment of the Staff of the Bureau of Competition and of Policy Planning of the Federal Trade Commission at 3 (recognizing the use of cumulative or duplicative petitions as a method for delaying competition from rivals) (Tab 1 ).

Alza's criticism of Mylan's fentanyl matrix system that will be its competitor in the United States is at odds with its own introduction of a fentanyl matrix system in Europe. Even Alza has

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<sup>1</sup> The requirement that generic equivalents OxyContin® adopt a risk minimization plan is neither surprising, nor a valid precedent for this situation, because OxyContin®, unlike Duragesic®, was itself already subject to a risk minimization plan.

<sup>2</sup> Alza's patent on Duragesic® expired on July 23, 2004 and it loses any possible applicable exclusivity on January 23, 2005.

to admit that there are advantages to matrix systems, including the elimination of dangerous gel leakage, which has led to recall of Duragesic®. Alza Petition at 2. Alza has introduced its matrix system in Europe and, as it enters each new market with its matrix product, it removes the reservoir product from that market. Alza Petition at 3. Alza's matrix system (sold by Janssen) uses a different material to construct the matrix than the Mylan FTS, but is equally subject to being cut into smaller pieces and has no rate control membrane. Even more surprising is that Alza's matrix system as sold in Europe has a drug loading significantly greater than Duragesic® or the Mylan FTS. This use of a system with substantially higher drug loading is inconsistent with Alza's repeated assertions that minimizing drug loading was essential to addressing abuse concerns. See Testimony of Dr. Mary Southam, Alza's Vice President of Technology Assessment (Exhibit 2 to Flynn Declaration). Alza has brought the advantages of fentanyl matrix systems to European patients, but now wants to interfere with American patients' access to that same technology. If, as Alza asserts here, matrix systems are inherently less safe than the Duragesic® reservoir design, then its actions in substituting its matrix system for its reservoir system would be unconscionable.

Alza asks FDA, on the basis of no evidence, to take two steps FDA has not taken before: (1) to treat a generic fentanyl transdermal system as a different dosage form based on its design and mechanism of release and (2) to require a generic drug to adopt a risk management program where the referenced drug has no such program. Because Alza's Petition is nothing more than a transparent attempt to interfere with Mylan's introduction of a generic fentanyl transdermal system, it should be denied immediately.

- **FDA Has Already Rejected Alza's Position That Systems Using Different Technology Are Different Dosage Forms.**

The Office of Generic Drugs has never required that generic extended release products, including transdermal systems, have the same release mechanisms as the referenced drugs. For example, FDA concluded that in the case of nifedipine the generic and referenced drug were not different dosage forms although they used very different release mechanisms. FDA concluded (and the court confirmed) that imposing a restriction that the generic and referenced products have the same rate control mechanism was unnecessary, as long as bioequivalence was established. In the realm of transdermal products, FDA has never treated generic systems as different dosage forms despite differences in system design. To the contrary, both nitroglycerin and nicotine drug-in-adhesive matrix systems were approved as generics to NDA-approved transdermal systems using different rate-control mechanisms.<sup>3</sup> Therefore, there is significant precedent that variation in design of two transdermal products does not warrant treating them as different dosage forms.

The alleged differences between its reservoir and the Mylan FTS that Alza asserts as the basis for its request that FDA treat the products as different dosage forms are not supported by

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<sup>3</sup> Specifically, FDA approved Mylan's drug-in-adhesive nitroglycerin patch as a generic to Ciba-Geigy's TransdermNitro®, which is said to contain a rate-controlling membrane. Likewise FDA approved Sano's drug-in-adhesive matrix nicotine patch as generic to the Habitrol patch, which is not a matrix system.

any evidence. Despite Alza's attempts to construct arguments to support its desired result for anticompetitive purposes, Alza's arguments fall apart when subjected to scientific review.

1. The Mylan FTS Does Not Pose A Risk On Stripped Skin.

Alza's first argument for treating the Mylan FTS as a different dosage form is that the Mylan FTS poses a different type of risk when applied to stripped skin. This argument assumes the validity of the assertions made in the petition filed by Dr. Steven L. Shafer (Docket No. 2004P-0340). Based purely on speculation and faulty scientific premises, the Shafer petition requested that generic FTS applicants be required to demonstrate bioequivalence to Duragesic® not only when the patch is applied to normal skin according to label directions, but also when it is applied to "stripped" skin contrary to those label directions. As addressed in detail in Mylan's response to that petition, Dr. Shafer incorrectly concludes that patients may be exposed to toxic levels of fentanyl in the absence of such a showing on stripped skin. Alza now points to the Shafer petition as grounds for its assertion that matrix and reservoir systems should be treated as different dosage forms. Alza Petition at 7.

To avoid burdening the agency with unduly repetitive filings, Mylan will not repeat herein the substance of its detailed response to the Shafer citizens' petition but has instead attached a copy of that response hereto at Tab 2. In summary, in that response, Mylan has requested that FDA deny the petition for at least the following reasons. First, while it has been well known for decades that skin that has repeatedly been stripped with adhesive materials is more permeable than intact skin, Dr. Shafer has failed to understand that the extent of stripping that is required to compromise the barrier properties of the skin cannot occur with simple application and removal of surgical tapes and bandages. Second, Dr. Shafer apparently has failed to appreciate that when skin stripping has occurred to an extent sufficient to compromise its barrier properties, it exhibits visible damage and irritation. Existing label instructions direct that patches not be applied to damaged or irritated skin. See *Final Printed Labeling for Duragesic®* (Approved May 20, 2003). Third, the studies upon which Dr. Shafer relies provide no data that is relevant to his conclusion that application of generic FTS on stripped skin may result in toxic levels of fentanyl. Last, the data upon which Dr. Shafer relies is derived from a study involving an experimental and unapproved fentanyl patch and not a generic FTS that was designed to be bioequivalent to Duragesic®. For the same reasons that the Shafer citizens' petition should be denied, the arguments set forth therein do not provide a basis for granting Alza's requested actions.

2. There Is No Evidence of Differences Between Duragesic® And The Mylan FTS With Respect To The Effect of Heat.

Alza's second argument in support of its request that the Mylan FTS be treated as a different dosage form than Duragesic® is that the Mylan FTS might release high amounts of fentanyl in the presence of heat. Like the FDA approved labeling for Duragesic®, the Mylan FTS labeling includes warnings about the effects of heat on the transdermal administration of fentanyl, as will the labeling for any other generic equivalent of Duragesic®. See *Approved Labeling for the Mylan FTS*. Alza offers no evidence that the risk of heat exposure is any higher than Duragesic® for either matrix systems in general or the Mylan FTS in particular. Indeed, Alza's

own testing apparently showed no tendency for delivery of excessive or potentially harmful doses of fentanyl from its matrix product, which like the Mylan FTS has no rate-controlling membrane. See Alza Petition at 8. Alza suggests, without presenting any support, that perhaps the result would be different for a matrix system using skin-permeation enhancers or with different drug loading. See Alza Petition at 8. However, the Mylan FTS (1) uses no skin permeation enhancers and (2) has lower fentanyl loads than the Janssen fentanyl matrix.<sup>4</sup> Thus, there is no reasonable basis to believe that the Mylan FTS is any more susceptible to the effects of heat than Duragesic®.

- **Nothing in Alza's Petition Supports the Conclusion that the Mylan FTS Poses a Greater Risk of Abuse or Diversion than Duragesic®.**

Alza also asks FDA to take the unprecedented step of requiring that a risk management program be instituted for the generic version of a product when the referenced drug has no risk management program in place.<sup>5</sup> Alza's Petition relies on three bases for its assertion that the Mylan FTS has a greater risk of abuse or diversion. First, Alza asserts that the ability to divide the Mylan FTS into smaller pieces (and the ability to avoid fatal doses associated with extracting fentanyl gel from Duragesic®) would lead to its use as a "party drug." Alza Petition at 4. Second, Alza asserts that fentanyl is easier to extract from matrix systems in certain solvents. Alza Petition at 5. Third, Alza asserts that its commissioned study of the desirability of opioids to potential abusers suggests that the Mylan FTS would be more prone to abuse than Duragesic®. These asserted bases for treating the Mylan FTS differently than Duragesic® fail any scientific scrutiny.

1. The Mylan FTS Would Not Be a Party Drug.

Echoing the petition filed by Drs. Brookoff and Voth, Alza asserts that because it can be cut into smaller sizes the Mylan FTS would be a more abusable drug than Duragesic®. The idea that the Mylan FTS cut into pieces would be a desirable party drug is simply incorrect. The speed with which an abuser receives a dose of opioid is an important aspect of its attractiveness as a recreational drug. See Goldman Decl. at ¶¶ 5-6 (Tab 3). Because of its robust rate-controlling properties, the Mylan FTS is particularly ill-suited to delivering opioids quickly.

Cutting a Mylan FTS into smaller pieces does not in any way increase the rate of fentanyl delivery from each square centimeter of the system. Flynn Decl. at ¶ 16. In fact, because dosing from transdermal systems is proportional to the surface area of the system, the effect of cutting

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<sup>4</sup> The Janssen matrix sold in Germany contains 4.2 mg in the 25mg/hr system – much more than the 2.5 mg contained in both Duragesic® and the Mylan FTS of the same dose..

<sup>5</sup> Should FDA come to the conclusion that a risk management program is warranted for all fentanyl transdermal systems, Mylan would, of course, cooperate in the development and implementation of an appropriate program. The implementation of such a program should not be an impediment, however, to the approval of the Mylan FTS.

the system into smaller pieces would be to reduce the possible fentanyl delivery from that system proportionally. Id. In other words, cutting a Mylan FTS in half would reduce its surface area by half and therefore halve the delivery rate and dose of fentanyl potentially delivered from that system.<sup>6</sup> In contrast, if Duragesic® were cut into pieces this would expose ready-to-abuse gel containing dissolved fentanyl, which is an immediate-release form of fentanyl capable of providing rapid dosing of fentanyl. Cutting the Mylan FTS into pieces would just result in lower dose, smaller pieces of drug-containing adhesive. Each piece would retain the matrix's rate control release properties.

Placing a Mylan FTS in the mouth rather than on the skin (whether it was cut into pieces or not) would not deliver fentanyl rapidly so as to make it an attractive target for abuse. Even if cut into pieces and placed in the mouth, the Mylan FTS matrix remains a slow-release delivery system and the basic mechanism of delivery of fentanyl does not change. See Flynn Decl. at ¶ 15 (Tab 4). Fentanyl still has to dissolve in the adhesive matrix and diffuse to the patch's releasing surface before partitioning into the oral fluids, a slow process controlled by fentanyl's solubility in and diffusion coefficient through the patch's adhesive matrix. Id.

The Mylan FTS would be a very inefficient vehicle for delivering fentanyl through the buccal membranes in the mouth. First, the silicone adhesive in the Mylan FTS would not adhere to the oral mucosa. See Flynn Decl. at ¶ 18. In fact, the extremely hydrophobic nature of that adhesive means that it is particularly ill-suited for maintaining contact between the matrix and the buccal membrane. Id. at 18-21. This conclusion is supported by the fact that products that are designed to adhere to oral surfaces use entirely different types of adhesives, ones that are extremely hydrophilic, not hydrophobic. Flynn Decl. at ¶ 21. Intimate contact between a matrix system and the membrane (whether it is skin or a mucosal membrane) is essential to allowing the system to deliver drug to the bloodstream. Id. at ¶ 18.

Because of the lack of adhesion, any fentanyl released by the system in the mouth is likely to result in extremely low concentrations in the saliva, which will in turn result in low transmucosal absorption, rather than moving into the bloodstream through the mucosal membranes. Flynn Decl. at ¶ 22. Fentanyl in the saliva that is swallowed will not have significant systemic effects because of the high first-pass metabolism of fentanyl. Id. at ¶ 23. Therefore, a potential abuser would not be able to place the Mylan FTS against the inside of his cheek and receive rapid delivery of fentanyl.

Second, the fentanyl base contained in the Mylan FTS would not be immediately released from the system if it were placed in the hydrophilic environment of the mouth. Flynn Decl. at ¶ 25. The Mylan FTS contains the base form of fentanyl, a highly water-insoluble component, in a water-insoluble silicone adhesive backed by a water insoluble polymeric film. Id. Most of the fentanyl base contained in the Mylan FTS is undissolved drug. Id. As a result, although some fentanyl would be released from the Mylan FTS into the mouth, that release would be far from an

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<sup>6</sup> The abuse of Duragesic® in this manner has been described on websites concerning illicit drug use, such as [www.erowid.org](http://www.erowid.org).

immediate release of the drug load. In fact, drug release would likely be quite slow because of the slow dissolution of fentanyl base in water. Id. at ¶¶ 24-25.

Dissolution data on the Mylan FTS confirms that it would not release fentanyl rapidly in the aqueous environment of the mouth. In dissolution testing, when placed in 500 ml water at physiologic pHs, the Mylan FTS released only 15 percent of its drug load in 30 minutes, and that release is linear over time.<sup>7</sup> Flynn Decl. at ¶ 24. Accordingly, it will take several hours for the majority of the drug to be released from the Mylan FTS. The volume of saliva contained in the oral cavity at any time is a very small fraction of the volume of water used in dissolution testing. In addition, fentanyl base is highly insoluble in water. As a result, the amount of fentanyl that could be released from the Mylan FTS in the buccal cavity of a user's mouth would be a very small fraction of the drug contained in the Mylan FTS.

It is neither practical nor convenient for any abuser to have the Mylan FTS, regardless of the size, in the mouth for several hours. As discussed above, since the patch would not adhere to the buccal membranes, any significant portion of fentanyl that is released in the mouth is likely swallowed with saliva and would enter the gastrointestinal tract. Because fentanyl has very high first pass metabolism, very little of the swallowed fentanyl would enter systemic circulation. Further, since the conditions for fentanyl release are unfavorable in the oral cavity, very little fentanyl would be absorbed by the user. As a consequence, if the Mylan FTS were placed in the mouth, very little fentanyl would reach the blood circulation. In contrast, the user cutting open a Duragesic® and removing the fentanyl-laden gel would not have to wait for the fentanyl to dissolve out of an adhesive matrix and, therefore, the majority of the fentanyl contained in the reservoir patch could be delivered into the bloodstream.

Based on these basic facts about the design of the Mylan FTS, the patch, if placed in the mouth, would provide a slow and steady release of fentanyl with low efficiency in reaching the bloodstream. See Flynn Decl. at ¶ 25. The literature on abuse of prescription drugs makes plain that the abuse and diversion potential of a drug is directly related to its ability to provide users with a rapid increase in the levels of drug inside the brain. See Declaration of H. Brian Goldman, M.D. ("Goldman Decl.") at ¶ 5. A rapid increase in opioid levels in the brain will trigger a rapid increase in dopamine in the brain, producing euphoria or pleasure of rapid onset. Id. Therefore, a system with a slow pattern of delivering opioids would not create a desirable rapid increase in the levels of the drug inside the brain and, therefore, would not be an attractive target for abusers. Id. at ¶ 6.

Thus, for the same reasons that the petition filed by Drs. Brookoff and Voth should be denied, there is no support for the action Alza requests and, therefore, this petition should be denied as well.

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<sup>7</sup> According to Alza's data, the slow dissolution of fentanyl transdermal matrices in water is also applicable to its matrix system. Alza Petition at 5.

2. Alza's Room Temperature Soak Test Is Not a Reasonable Comparison of Duragesic® and the Mylan FTS.

Alza purports to make certain statements about the extraction of fentanyl from the Mylan FTS based on its room temperature soak test of its own products. That testing provides no useful evidence for comparing the abuse potential for Duragesic® and the Mylan FTS.

First, Alza's analysis ignores the most fundamental difference in the reservoir and matrix designs. No potential abuser would ever need to use solvents to extract fentanyl from Duragesic® because the pure fentanyl-laden gel contained in a Duragesic® system could be removed by physical means much more easily. Unlike the Mylan FTS, the fentanyl in a Duragesic® system can be easily accessed by simply cutting the patch open and squeezing the gel from the reservoir or by withdrawing the gel from the reservoir with a syringe. Once a potential abuser has done so, he has access to a large amount of readily available fentanyl, which can then be dispensed in the desired amount. The amount of gel used can be easily titrated by the abuser. That process could be completed in a matter of minutes, not hours. Therefore, if one is comparing the abuse potential based on the amount of time or ease with which one could remove the active fentanyl from the physical constraints of the transdermal system, it is Duragesic® that is the more accessible source of fentanyl.

Second, Alza's testing was performed only on its own matrix design, which cannot be generalized to the Mylan FTS. Alza's study tested not a silicone adhesive matrix like that used in the Mylan FTS but an acrylic adhesive matrix with twice the drug loading, which may or may not have the same dissolution characteristics.

3. The Butler Study Is Fundamentally Flawed as Applied to the Fentanyl Matrix

To manufacture evidence to cite in support of its unprecedented request that a generic version of an opioid be subject to a risk management program not required of the manufacturer of the referenced drug, Alza commissioned a study purportedly designed to measure the attractiveness of different opioids to potential abusers. Alza Petition at 5.

Putting aside the questionable usefulness of a study for comparing other opioids, it is of no utility when applied to the fentanyl matrix system and, particularly for comparing Duragesic® and the Mylan FTS. The study determined 17 parameters for the attractiveness of drug products to abusers and then asked study subjects to assess the desirability of those drug products. One method of making this assessment was based on the study subjects' experience with the drugs. As the study authors themselves recognized, "since the fentanyl matrix patch was not commercially available at the time of testing, no one in these samples could have had experience with this substance." Butler Study at 75 (Attachment 4 to Alza Petition). In other words, subjects

were asked to assess the desirability of fentanyl matrix systems based on their own experiences without having had any experience with the product.<sup>8</sup>

A second method of assessing the attractiveness of opioids is no more reliable with respect to the fentanyl matrix system. Under that method, the Alza-commissioned researchers provided the test subjects with standardized descriptions of the opioids being studied. The effect of the descriptions would be particularly powerful on the results for the fentanyl matrix system because none of the subjects being questioned could have had personal experience with that product. What Alza did not include in the materials submitted to the agency is any description of how the fentanyl transdermal matrix system was described to the test subjects. One cannot determine from the materials submitted what potential abusers were told about the characteristics of the fentanyl matrix system. Alza has taken the position in its Petition that the fentanyl matrix system provides easily divisible doses of rapidly released fentanyl. If the test subjects were told, for example, that the fentanyl matrix system would work quickly, that would certainly influence the results of the survey. Likewise, if Duragesic® were described as being “designed in a way that is difficult to abuse to get a high” and fentanyl transdermal matrix systems were described as not being so designed, the survey results would certainly be affected by that misinformation.

Alza’s supposed evidence that the Mylan FTS would be more attractive to potential abusers than Duragesic® is thus based entirely on opinions from study participants who had either a total lack of knowledge about the actual characteristics of those systems or on Alza’s provision to the participants of its own inaccurate or biased description of the characteristics of the Mylan FTS. Therefore, this study cannot be viewed as providing any credible evidence concerning the attractiveness of the Mylan FTS to potential abusers.

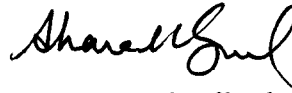
### CONCLUSION

For the reasons set forth herein, Alza’s Petition should be denied in all respects.

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<sup>8</sup> Indeed, it calls into question the accuracy of all the responses that nearly a quarter (23.7%) of the subjects in the developmental sample and nearly a fifth (19.5%) of the subjects in the confirmation sample indicated they had had experience with the fentanyl matrix patch. Butler Study at 75.

Respectfully submitted,



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